Caspian Journal of Pediatrics
Babol University of Medical Sciences
e-ISSN: 2383-3106

Factors Influencing Outcome of Neonates with Perinatal Asphyxia in a Tertiary Care Hospital

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Article Info.

Article type:
Research Article

Received: 20 Oct. 2023
Revised: 29 Feb. 2024
Accepted: 5 March 2024
Published: 18 May 2024

Keywords:
Apgar Score,
Asphyxia,
Birth Weight,
Gestational Age

ABSTRACT

Background and Objective: Perinatal asphyxia is one of the major contributors to neonatal mortality in developing countries. Identification of factors influencing the early outcome in perinatal asphyxia will help to plan necessary interventions. The aim of this study was to evaluate the factors influencing the early outcome of asphyxiated neonates.

Methods: This retrospective cohort study was conducted on asphyxiated neonates admitted to the neonatal intensive care unit (NICU) of a tertiary Medical college hospital in Chennai, Tamilnadu, India, from January to December 2016. The relationship between the risk factors and early outcome of asphyxia was analyzed using a statistical chi-square test. A multivariate analysis was performed to determine the factors influencing the outcome. A value of $p<0.05$ was considered significant.

Findings: Of 346 asphyxiated neonates, 42 (12.1%) died. Multivariate analysis revealed that factors like parity (OR:0.018, p-value=0.01), birth weight (OR:3.217, P-value=0.04), meconium stained liquor (MSL) (OR:3.217, p-value=0.03), APGAR score at five minutes (OR:0.533, p-value=0.04), shock (OR:4.123, p-value=0.01), and abnormal cranial ultrasound (OR:2.390, p-value=0.03), and mechanical ventilation (OR:13.496, p-value=0.03), were significantly associated with outcome.

Conclusion: The current study revealed that maternal factors such as parity, intrapartum factors like MSL, low five-minute Apgar score, neonatal factors like birth weight, shock, abnormal cranial ultrasound, and mechanical ventilation had a significant impact on the mortality of neonates with perinatal asphyxia. As many of these factors are modifiable, better intrapartum monitoring and timely initiation of corrective measures may help to improve the early outcome of asphyxiated neonates.

Cite this article: Devimeenakshi K, SathishKumar K. Factors Influencing Outcome of Neonates with Perinatal Asphyxia in a Tertiary Care Hospital. *Caspian J Pediatrs* March 2024; 10: e1.

[DOI: 10.22088/CJP.BUMS.10.0.1]

Introduction

Perinatal asphyxia is a major cause of neonatal mortality in developing countries [1]. Perinatal asphyxia is responsible for about a quarter of all neonatal deaths worldwide. Approximately, 4 million neonates are asphyxiated at birth each year, resulting in 2 million neonatal deaths and intrapartum stillbirths [2]. In underdeveloped countries, asphyxia is still the leading cause of neonatal mortality and morbidity. Moreover, 40% of neonatal deaths occur during labor or on the first day of life [3]. Birth asphyxia (20%) is one of the major causes of neonatal mortality along with prematurity (35%) and sepsis (33%). Though India has made progress in reducing neonatal mortality and its share of global neonatal mortality has fallen to less than one-fifth of total neonatal mortality, there is still scope for improving the quality of healthcare delivery [4]. In India, the average neonatal mortality rate is 19.11 per 1000 live births, with wide variations in urban (12 per 1000 live births) and rural (23 per 1000 live births) mortality rates. As the majority of neonatal deaths fall into the category of early neonatal mortality, targeted treatment in the period around birth with proven effective interventions and high-quality care for sick newborns can prevent neonatal deaths [5].

Perinatal asphyxia is a combination of hypoxia and ischemia occurring in the fetus or neonate. The asphyxia insult can occur in the prenatal or intrapartum period [6]. Asphyxia damages not only the central nervous system, but also other organs. The redistribution of cardiac output in response to asphyxia preserves the oxygen delivery to vital organs at the expense of organs like the intestines, kidneys and skin. This leads to hypoxia and ischemia in these organs, which can result in multi-organ failure [7]. The changes in the central nervous system can be recognized by the clinical picture of encephalopathy, which can vary in severity.

Since asphyxia is associated with immediate and long-term morbidities, it is necessary to identify the modifiable factors to minimize the consequences of asphyxia. Several studies have investigated the risk factors for asphyxia. Maternal factors such as age, parity and antepartum hemorrhage, neonatal factors like gestational age and birth weight as well as intrapartum factors for instance meconium stained liquor (MSL), duration of second stage and mode of delivery have been identified as associated with birth asphyxia [8, 9, 10]. However, despite advances in obstetric care and intrapartum monitoring, asphyxia is still a major cause of neonatal mortality. The long-term effects of perinatal asphyxia have been extensively studied. Nevertheless, there is a paucity of research is available on strategies to modify disease progression during post-resuscitation care to influence early outcome and reduce mortality. With this in mind, the aim of this study was to analyze the risk factors that influence early outcome in neonates with perinatal asphyxia.

Methods

Study design and sample

This was a retrospective cohort study of all neonates, both preterm and term, delivered in a tertiary Medical College Hospital in Chennai,Tamil Nadu, India, who were resuscitated in the neonatal intensive care unit (NICU) between January 2016 and December 2016. The possibility of perinatal asphyxia was considered in those neonates who had clinical features of neonatal encephalopathy after a significant perinatal history with an Apgar score of <7 in the first minute of life or who were not spontaneously breathing at birth and required positive ventilation [11].

As in other resource-poor settings, birth asphyxia was defined as a failure of spontaneous respiration at birth with a 1-minute Apgar score <7.00 [11]. The Apgar score was assigned after one minute and after five minutes. If the five-minute score was less than 7, the score was repeated every 5 minutes to 20 minutes. The use of biochemical criteria for fetal acidosis in the umbilical cord blood, although important for diagnosis, was not available due to limited resources. The neonatal intensive care unit of our hospital admits all neonates with an Apgar score of less than 7 after five minutes for observation and necessary intensive care. However, since the present study was a retrospective one, only those neonates whose clinical findings and laboratory parameters were suggestive of encephalopathy and / or multiorgan

[DOI: 10.22088/CJP.BUMS.10.0.1]

dysfunction secondary to birth asphyxia, were included in the current study, and data were collected only after discharge or death of the neonate. Arterial blood gas analysis was performed as part of the routine evaluation of these neonates in the NICU.

The sample size was not calculated in advance. Nevertheless, the post-hoc calculation based on the prevalence of convulsions in non-survivors and survivors of 30 % and 83% in a study by Meshram et al. [12], the available study sample of 42 neonates who died and 304 neonates who were discharged, gives a power of 95% at a 95% confidence level.

Inclusion criteria

Neonates admitted for post-resuscitative care with clinical and /or laboratory evidence of neonatal encephalopathy, and / or multi-organ dysfunction in the setting of hypoxic ischemic encephalopathy.

Exclusion criteria

Neonates admitted for post-resuscitation care but diagnosed otherwise by clinical examination and /or laboratory tests, newborns delivered outside the hospital extramurally and those with major congenital malformations were excluded from the present study.

Data collection

Data were collected in the prepared proforma by the principal investigator from the case records of neonates who were treated in the NICU with a final diagnosis of hypoxic ischemic encephalopathy and were discharged after successful treatment or died despite treatment.

Maternal factors such as maternal age, parity, mode of delivery, presence of MSL and so on were collected. The neonatal factors like birth weight, gestational age, severity of birth asphyxia (measured by Sarnat & Sarnat grading), need for mechanical ventilation, shock, cranial ultrasound abnormalities and associated morbidities like sepsis were recorded. Maternal, intrapartum and neonatal factors were compared between neonates who died and those who fared better.

Statistical Analysis

All data were analyzed using SPSS 20. The descriptive statistics included the calculation of percentages and mean values. The univariate analysis of various parameters was compared with the result using the chi-square test. Multivariate analysis was performed to estimate the risk and expressed as odds ratio with 95% confidence interval [OR (CI)]. A p-value <0.05 was considered statistically significant.

Results

There were 5603 deliveries during the study period. During this period, there were 3066 intramural admissions to the neonatal intensive care unit, including neonates admitted to the NICU and also for observation. As the ward is located in a tertiary referral hospital, many of the high-risk mothers were referred for delivery. Of these, 346 newborns with birth asphyxia were admitted for post resuscitative care and included in this study.

This accounted for 11.3 % of admissions during the study period. Of these, 42 (12.1%) neonates died and 304 (87.9%) neonates were discharged and followed-up in the high-risk neonatal clinic. The mortality rate for asphyxiated female neonates was significantly higher 25(16.1%) than for male asphyxiated neonates 17(8.9%) (p=0.041).

It was found that among the asphyxiated neonates, 267(77.2%) neonates were term. The mortality rate of 30(71.4%) was significantly higher in asphyxiated preterm infants (p=0.000). It was observed that mortality increased with decreasing gestational age.

Among the asphyxiated newborns in the current study, 225 (65%) ones had a birth weight >2.5 kg. Mortality increased with decreasing birth weight, which was statistically significant (p=0.000).

About 162 (46.8%) of the asphyxiated neonates were delivered vaginally. Death was observed more frequently in asphyxiated newborns delivered by caesarean section. However, this difference was not statistically significant (p =0.134).

Of the asphyxiated neonates, most 196(56.6%) were born to primiparous mothers. It was found that

[DOI: 10.22088/CJP.BUMS.10.0.1]

mortality was significantly higher with increasing parity (p=0.005).

Of the mothers of the asphyxiated neonates, 167(48.3%) were between 21 and 25 years old. Mortality due to birth asphyxia was highest (40%) in infants born to mothers >35 years of age (Table 1).

The mean maternal age was comparable in both groups. The mean birth weight was 1.7 kg in the newborns who died compared to 2.74 kg in those who recovered. It was found that the mean length of hospital stay was 4.4 days in the neonates who died compared to 8.3 days in those who recovered.

The Apgar score at five minutes revealed that 146 (42.2%) newborns had a score of less than 3. Mortality was high when the five-minute Apgar score was less than three [36(24.7%)], and this was found to be statistically significant (p =000).

Neonatal risk factors investigated included the presence of seizures, shock, comorbidities such as sepsis, abnormal cranial ultrasound and the need for mechanical ventilation.

When comparing the results in asphyxiated neonates with seizures, it was found that 12(18%) neonates with seizures had died compared to only 30(10.8 %) neonates without seizures, but this was not statistically significant (P= 0.107).

Among newborns with shock, a highly significant number of 37(54.4%) deaths were found (p=0.000). The mortality rate was higher in asphyxiated neonates requiring mechanical ventilation [8(61.5%)] than in neonates without shock [34(10.2%)], which was statistically significant (P=0.000).

When comparing the results in neonates with sepsis, it was found that the situation had improved in 29 (80.6%) neonates. The mortality rate was higher in asphyxiated neonates who also had sepsis and the observed difference was not significant (p=0.156). When comparing the results in newborns with abnormal cranial ultrasound, it was found that 5(35.7%) of them died. The abnormal cranial ultrasound finding was intracranial hemorrhage. Mortality was significantly increased in newborns with abnormal cranial ultrasound findings (p=0.006) (Table 2).

Multivariate analysis revealed that factors like parity (OR=0.018, p value= 0.01), birth weight (OR=3.217, p value =0.04), MSL (OR=3.217, p value= 0.03), APGAR score at five minutes (OR=0.533, p value= 0.04), shock (OR=4.123, p value= 0.01), and abnormal cranial ultrasound (OR=2.390, p value= 0.03), and mechanical ventilation (OR=13.496, p value =0.03), were significantly associated with outcome (Table 3).

Discussion

The aim of this study was to analyze the factors influencing early outcome in neonates with perinatal asphyxia. Maternal and neonatal factors were investigated and their association with outcome was assessed. Of the various factors studied, birth weight, parity, MSL, Apgar score at five minutes, abnormal cranial ultrasound and the need for mechanical ventilation had a significant impact on the early outcome of neonates with perinatal asphyxia.

Our study showed that among the asphyxiated newborns, most were born to primipara mothers. Similar observations were made in previous studies [13, 14, 15, 16]. We observed that parity was significantly associated with outcome among asphyxiated neonates. However, contrary findings were reported by Gebreheat G et al. [17] in their study. Primipara mothers were more prone to malpresentations and prolonged or obstructed labor, making them more prone to have asphyxiated neonates [18].

In the present study, the majority of asphyxiated neonates were born with clear liquor (65.9%) followed by MSL (33.2%). Although blood-stained liquor was only a minority (0.9%), mortality was highest in this group. Mortality in the group with MSL (8.7%) was not higher than in the group with clear liquor (12.7%). In a study by Sahib HS, et al., although meconium-stained amniotic fluid (MSAF) was a common risk factor, occurring in 14.05% of cases, it was not significantly associated with mortality in asphyxiated neonates [13]. Ibrahim MH

[DOI: 10.22088/CJP.BUMS.10.0.1]

Table 1. Neonatal and maternal factors among asphyxiated babies

Parameter		Discharge (%) N=304	Death (%) N=42	Total (%) N=346	P-Value
Gender	Male	174(91.1)	17(8.9)	191(55.2)	0.041
	Female	130(83.9)	25(16.1)	155(44.8)	
Gestational Age	>37 weeks	255(95.5)	12(4.5)	267(77.2)	0.000
	34-37 weeks	25(80.6)	6(19.4)	31(9)	
	32-34 weeks	12(75)	4(25)	16(4.6)	
	30-32 weeks	10(62.5)	6(37.5)	16(4.6)	
	28 -30 weeks	1(16.7)	5(83.3)	6(1.7)	
	<28 weeks	1(10)	9(90)	10(2.9)	
Birth Weight	<1 kg	1(12.5)	7(87.5)	8(2.3)	0.000
	1-1.5 kg	5(23.8)	16(76.2)	21(6.1)	
	1.5- 2.5kg	83(90.2)	9(9.8)	92(26.6)	
	>2.5 kg	215(95.6)	10(4.4)	225(65)	
Mode of Delivery	Vaginal	145(89.5)	17(10.5)	162(46.8)	0.134
	LSCS	134(85.4)	23(14.6)	157(45.4)	
	Forceps	24(96)	1(4)	25(7.2)	
	Assisted breech	1(50)	1(50)	2(0.6)	
Liquor	Clear	199(87.3)	29(12.7)	228(65.9)	0.000
	Meconium stained	105(91.3)	10(8.7)	115(33.2)	
	Blood stained	0(0%)	3(100)	3(0.9)	
Obstetric Score	Primi	180(91.8)	16(8.2)	196(56.6)	0.005
	Gravida2	82(88.2)	11(11.8)	93(26.9)	
	Gravida3	31(73.8)	11(26.2)	42(12.1)	
	Gravida4	8(80)	2(20)	10(2.9)	
	Gravida5	3(60)	2(40)	5(1.4)	
Maternal Age	<20 years	41(82)	9(18)	50(14.5)	0.968
	21-25 years	151(90.4)	16(9.6)	167(48.3)	
	26-30years	92(87.6)	13(12.4)	105(30.3)	
	31-35years	17(89.5)	2(10.5)	19(5.5)	
	>35years	3(60)	2(40)	5(1.4)	

Table 2. Neonatal factors influencing outcome of asphyxiated neonates

Factors		Discharged (%) N=304	Death (%) N=42	Total (%) N=346	P-Value
Apgar 5	<3	110(75.3)	36(24.7)	146(42.2)	0.00001
	>3	194(97)	6(3)	200(57.8)	
Seizures	Yes	55(82)	12(18)	67(19.4)	0.107
	No	249(89.2)	30(10.8)	279(80.6)	
Shock	Yes	31(45.6)	37(54.4)	68(19.7)	0.000
	No	273(98.2)	5(1.8)	278(80.3)	
Mechanical ventilation	Yes	5(38.5)	8(61.5)	13(3.8)	0.000
	No	299(89.8)	34(10.2)	333(96.2)	
Sepsis	Yes	29(80.6)	7(19.4)	36(10.4)	0.156
	No	275(88.7)	35(11.3)	310(89.6)	
Abnormal cranial ultrasound (Intracranial hemorrhage)	Yes	9(64.3)	5(35.7)	14(4)	0.006
	No	295(97)(88.9)	37(11.1)	332(96)	
Duration of stay	<1 week	181(83.8)	35(16.2)	216(62.4)	0.002
	>1 week	123(94.6)	7(5.4)	130(37.6)	-

Table 3. Multivariate analysis association between individual factors and outcome

Factor	Odds ratio	95% CI		P-Value
		Lower	Upper	
Gestational age	11.975	0.647	221.628	0.77
Parity	0.018	0.001	0.534	0.01
Birth weight	3.217	1.041	9.936	0.04
Meconium stained liquor	3.217	1.017	9.936	0.03
Mechanical ventilation	13.496	2.841	64.123	0.03
APGAR5	0.533	0.291	0.976	0.04
Shock	4.123	2.356	8.674	0.01
Abnormal cranial Ultrasound (Intracranial hemorrhage)	2.390	1.165	10.983	0.03
Gender	1.635	0.521	6.292	0.10

[DOI: 10.22088/CJP.BUMS.10.0.1]

et al. also found in their study that MSAF was a significant risk factor in asphyxiated neonates [19]. A previous study has shown that morbidity and mortality was higher in neonates born with thick MSL than those born with thin MSL [20]. MSAF is thought to represent the fetal response to hypoxic stress leading to the release of arginine vasopressin from the fetal pituitary gland which stimulates colonic smooth muscle, hyperperistalsis and anal sphincter relaxation. MSAF is independently correlated with the risk of adverse neonatal outcomes such as meconium aspiration syndrome, persistent pulmonary hypertension and hypoxic ischemic encephalopathy [21]. Infants with MSAF had low Apgar scores, and the number of neonates requiring intensive care was higher in the MSL group than in the clear liquor group [31(21.5%) versus 18(6.2%)]. Newborns born with MSL had a 2.5-fold higher risk of dying in the first week of life. The incidence of birth asphyxia, neonatal sepsis and NICU admissions was statistically higher in neonates born with meconium-stained fluid than in those born with clear liquor [22].

The current study indicated that most of the asphyxiated neonates were delivered vaginally (46.8%) or by cesarean section (45.4%). Other methods such as forceps (7.2%) and assisted breech (0.6%) deliveries were minimal. However, it was found that mortality was highest in newborns born by assisted breech delivery (50%), followed by cesarean section (14.6%). Mortality was lower in the group delivered vaginally (10.5%). In the study by Lohan R et al., [23] 64% of neonates with birth asphyxia were delivered vaginally. Nevertheless, previous studies have reported that the majority of asphyxiated infants were delivered by cesarean section [14, 15]. Another study found that assisted deliveries were common in asphyxiated newborns [16]. The increased risk of asphyxia in neonates delivered by cesarean section was attributed to the fact that mothers with obstetric complications reported to the health facility too late or performed the cesarean section too late. The increased risk in neonates born by assisted vaginal delivery was due to the pressure exerted by the forceps and vacuum on the fetal brain, leading to asphyxia and intracranial hemorrhage [24]. Previous studies have shown that neonates born by instrumental delivery were more than four times more likely to develop birth asphyxia than those delivered spontaneously vaginally [25]. In newborns delivered by cesarean section, elective cesarean section was found to be inversely related to encephalopathy, while emergency cesarean section was a risk factor for birth asphyxia [26]. An increased incidence of birth asphyxia in cesarean and instrumental deliveries could be due to the presence of fetal distress that may have warranted one of these delivery types.

In the ongoing study, it was found that among asphyxiated neonates, male gender, term delivery and newborns with a birth weight of >2.5 kg were the most common. Similar observations were also made in previous studies [13, 14, 16, 23]. The present study represented that mortality was higher in asphyxiated newborns with low birth weight, which is consistent with a study in south eastern Nigeria, where 34 (73.9%) of the asphyxiated low birth weight neonates died, while mortality among normal birth weight neonates was 23 [(23.7%), p<0.001] [27]. The results of this study were also similar to our findings in relation to gestational age, where mortality [41 (78.8%)] was significantly higher in preterm infants compared to term infants [15 (17.2%), p <0.001].

We observed that among asphyxiated neonates, deaths were more common in those who had seizures (18%), sepsis (19.4%), abnormal cranial ultrasound (intracranial hemorrhage) (35.7%), and shock (54.4%).

In the present study, it was observed that mortality was higher in asphyxiated neonates who developed seizures (18%). Meshram RM [12] found in their study that neonates who presented with convulsions were significantly associated with higher mortality. Previous study indicated that neonates who had suffered from birth asphyxia and moderate hypoxic ischemic encephalopathy develop clinical and electrographic seizures. Both seizure burden and time to complete oral feeding are useful in predicting the long-term outcome of these infants [28]. A study by Millaer SP et al. has revealed that the severity of seizures in newborns with perinatal asphyxia is independent of brain damage and is not limited to structural damage detectable by MRI [29]. In a

[DOI: 10.22088/CJP.BUMS.10.0.1]

previous study, it was observed that poorly controlled seizures, prolonged duration of labor, and the onset of seizures within 72 hours were identified as independent predictors of poor neonatal outcome. The odds of poor outcome were 4.3 times higher in neonates with seizures delivered during a prolonged labor (>24 hours), with an adjusted odds ratio of 4.3 (95% CI 2.2–8.8) and a p-value of 0.003. The odds of poor outcome were also 3.7 times higher in neonates with early onset seizures (<72 hours) with an adjusted odds ratio of 3.7 (95% CI 1.6–8.5), and a p-value of 0.007 [30].

In the present study, mortality was found to be higher in asphyxiated neonates who developed shock (54.4%). Asphyxiated neonates may have decreased cardiac output with ventricular myocardial dysfunction, decreased left ventricular preload secondary to pulmonary hypertension, and/or decreased ability to regulate vascular tone (vasoplegia). Although the main physiologic adaptation of the cardiovascular system to hypoxia is the redistribution of blood flow to the vital organs (heart and brain), this adaptation does not occur in the case of severe asphyxia because both the brain and myocardium develop ischemic lesions. It is well established that vasoconstriction leads to increased peripheral resistance, and the high resistance in the fetal circulation short-circuits blood to the placenta with low resistance, resulting in decreased circulating blood volume [31]. As Barberi et al. have demonstrated, newborns with severe asphyxia who present with signs of heart failure have an increased early neonatal mortality [32]. Therefore, it is essential to recognize the severity of cardiac involvement early and take measures to minimize further damage to the myocardium.

In the present study, it was observed that mortality was higher in asphyxiated neonates who were mechanically ventilated. In the study by Giannakis et al. it was found that the severity of asphyxia injury was higher in neonates who required intubation. The need for mechanical ventilation was significantly higher in newborns with more severe asphyxia. In ventilated neonates, level of encephalopathy and increased oxygen supplementation were significantly higher in the group with adverse short-term outcomes [33]. Asphyxia was the most common indication for mechanical ventilation in neonates (30.1%). However, asphyxia was not a significant predictor of outcome (p value 0.648) [34]. In the study of Iqbal Q et al., no statistically significant difference in mortality was found in neonates who were resuscitated compared to those who were not. Although severe perinatal asphyxia has a high mortality rate compared to mild and moderate perinatal asphyxia, improved resuscitation measures at the time of birth and early referral for such babies appear to have led to an improvement in survival for all resuscitated and subsequently ventilated neonates [35].

In the current study, mortality was found to be higher in asphyxiated neonates who developed sepsis (19.4%). Multivariate analysis illustrated that birth asphyxia was one of the factors significantly associated with neonatal sepsis (p value <0.05). Neonatal asphyxia favors systemic infections due to inhibited leukocyte activity and microbicidal activity of polymorphonuclear cells. Neonatal asphyxia increased the risk of early-onset neonatal sepsis with a four-fold positive blood culture result (OR = 4.102; 95% CI 1.04-16.14) [36].

In the present study, mortality was higher in asphyxiated neonates who had abnormal cranial ultrasound findings. In the ongoing study, intracranial hemorrhage was the only abnormal finding. Ganesan D et al. found that 70% of infants with birth asphyxia had normal cranial ultrasound findings, 12% of newborns had cerebral edema, 9.3% had white matter hyperintensities, 4% had intracerebral hemorrhage and 2.6% had hydrocephalus [37].

The analysis of the length of stay in both groups of newborns showed that the average length of stay was shorter in the newborns who died (4.4 days) than in those who recovered (8.3 days). The differences in time to recovery may be due to differences in severity of illness at admission, birth weight, gestational age and various morbidities of the neonates during hospitalization. Getanesh F B et al. indicated that low birth weight, severity of HIE, thrombocytopenia and seizures were predictors of time to recovery [38].

[DOI: 10.22088/CJP.BUMS.10.0.1]

The limitations of the ongoing study are that it was a retrospective study and limited to a single center. Arterial blood gas analysis in cord blood to document biochemical evidence of asphyxia was not performed due to resource limitations.

Conclusion

The ongoing study revealed that factors such as birth weight, parity, MSL, Apgar score at five minutes, neonatal morbidities such as the presence of shock, abnormal cranial ultrasound and the need for mechanical ventilation significantly influenced the early outcome of infants with perinatal asphyxia.

Acknowledgments:

The authors would like to thank the Medical records Department for their valuable support in the conduct of the study.

Ethical Considerations

This study was initiated after Institutional Ethics committee approval (Protocol ID No25/2017, meeting of 17.04.2017)

Funding

There was no financial support for this research.

Conflict of interest

There is no conflict of interest.

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